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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,540	09/23/2003	Robert Terkeltaub	UCSD1570-1	4639

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DLA PIPER LLP (US)
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,540	TERKELTAUB, ROBERT	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 14* is/are pending in the application.

4a) Of the above claim(s) *7 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 1 and 5 have been amended, and claims 11-13 have been canceled as requested in the amendment filed on 10 November 2008. Following the amendment, claims 1-3, 5-10 and14 are pending in the instant application.

Claims 7 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 30 January 2007.

Claims 1-3, 5, 6 and 8-10 are under examination in the instant office action.

Withdrawn Rejections

The rejection of claims 1-3, 5, 6 and 8-10 under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al. and Oliverio et al., further in view of Heyninck et al. and Grey et al. is withdrawn in response to the amendment to the claims, which deleted "A20."

The rejection of claims 11-13 under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al. and Oliverio et al., further in view of Heyninck et al. and Grey et al. is withdrawn as moot in response to the cancellation of said claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyasaka et al. (Nitric oxide and inflammatory arthritides. Life Sci. 1997;61(21):2073-81).

Claims 1-3 are directed to a method for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix. Claim 5, 6 8 and 9 are directed to a method for inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte, comprising contacting the chondrocyte with an effective amount of an inhibitor of a TNFα receptor-associated signaling factor (TRAF), wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA), thereby inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte.

The Miyasaka et al. reference teaches that administration of the nitric oxide synthase inhibitor NMMA successfully blocks the onset of arthritis in rats (entire

document, e.g. abstract) and that nitric oxide stimulates apoptosis in chondrocytes (p.2076 under heading "NO Production in Cartilage"). It is noted that the instant claims only recite one active method step, i.e. administering NMMA. The remaining limitations recited by the claims are not active method steps, i.e. thereby suppressing pathological calcification in the cartilage matrix (recited by independent claim 1), wherein the inhibition of activation is accomplished by blocking production of a member selected from the group consisting of interleukins IL-1, IL-8, nitric oxide donor Noc-12, peroxynitrite generator Sin-1, tumor necrosis factor α (TNFα), and S100 family of proteins (recited by dependent claim 2), wherein the inhibition of activation is accomplished by blocking TNFα receptor-associated signaling factors (TRAFs), TRAF2 and TRAF6 (recited by dependent claim 3), thereby inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte (recited by independent claim 5) and wherein the inhibitor is an inhibitor of IL- 1, Noc-12, Sin-1, tumor necrosis factor α (TNFα), and/or TNFα receptor-associated signaling factor (TRAFs), TRAF2 and TRAF6 (recited by dependent claim 6). Rather, these are statements of phenomena that necessarily occur after the administration step. Although the Miyasaka et al. reference does not explicitly appreciate these remaining limitations of claims 1-3, 5 and 6, these would nonetheless be inherent outcomes induced by administering NMMA. Applicants are reminded that chemical compounds and their properties are inseparable (In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)). That is, since the Miyasaka et al. reference teaches the all

of the materials required to practice the claimed invention, i.e. the subjects in need thereof (rats with arthritis), the inhibitor (NMMA), the cartilage matrix (within the subjects) which includes chondrocytes, the reference inherently teaches the remaining limitations of claims 1-3, 5 and 6. Further, since the reference teaches that NMMA is effective in treating arthritis, the methods set forth therein must have the recited effects. The reference teaches administration *in vivo* (as set forth above), thus meeting the limitations of claim 9 and teaches administration *in vitro* (p.2076, under heading "NO Production in Synovial Tissue"), thus meeting the limitations of claim 8. Since the reference teaches all the limitations of the claims (both expressly and inherently), claims 1-3, 5, 6, 8 and 9 are anticipated by Miyasaka et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5, 6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al. (citation N on IDS dated 24 November 2004), in view of Hashimoto et al. (citation H on IDS dated 24 November 2004), further in view of Miyasaka et al. (Nitric oxide and inflammatory arthritides. Life Sci. 1997;61(21):2073-81).

Claims 1-3 are directed to a method for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix. Claim 5, 6 and 8-10 are directed to a method for inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in a chondrocyte, comprising contacting the chondrocyte with an effective amount of an inhibitor of a TNFα receptor-associated signaling factor (TRAF), wherein the inhibitor is NG-monomethyl-L-arginine acetate (NMMA), thereby inhibiting TGase activity of zymogen Factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase) in the chondrocyte.

The Nurminskaya et al. reference teaches that transglutaminase and FXIIIa are unregulated during chondrocyte hypertrophy and calcification (p.1135) and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes (e.g., p.1136, ¶3, p.1142, ¶5), as in the instant claims 1 and 5. Further, the Nurminskaya et al.

reference teaches chondrocytes from a chondrocyte-derived cell line (p.1136, ¶5), as in the instant claim 10.

Although the teachings of Nurminskaya et al. suggest that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states, the reference does not explicitly teach such. However, upon reading the disclosure of the Nurminskaya et al. reference, the skilled artisan would have recognized the desirability of developing improved methods for treating pathological calcification of the cartilage matrix. Furthermore, the Hashimoto et al. reference teaches that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are involved in human osteoarthritis (pp.1632-1633), as in the instant claim 1. The Hashimoto et al. reference also teaches that future treatment options, (e.g., apoptotic inhibitors), would alleviate chondrocyte apoptosis and thus matrix calcification and degradation (p.1638, final paragraph). The Hashimoto et al. reference teaches that mediators of necrosis and apoptosis in chondrocytes include IL-1, TNFα and nitric oxide (p.1632, ¶3), as in the instant claim 2. Both references teach *in vitro* and *in vivo* methods (entire documents), as in the instant claims 8 and 9.

Although the teachings of Hashimoto et al. suggest that inhibiting nitric oxide would decrease apoptosis in pathological states, the reference does not explicitly teach administering a nitric oxide inhibitor. However, the Miyasaka et al. reference teaches that the nitric oxide synthase inhibitor NMMA successfully blocks the onset of arthritis in rats *in vivo* (entire document, e.g. abstract) and that nitric oxide stimulates apoptosis in

chondrocytes (p.2076 under heading "NO Production in Cartilage"), as in the instant claims.

As evidenced by the Nurminskaya et al. reference, the skilled artisan would have known that inhibiting tTGase and FXIIIa to reduce apoptosis would alleviate disorders of pathological calcification and degradation of the cartilage matrix. As evidenced by the Hashimoto et al. reference, the skilled artisan would have known that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are involved in human osteoarthritis and that treatment options comprise apoptotic inhibitors and nitric oxide inhibitors. As evidenced by the Miyasaka et al. reference, the skilled artisan would have known that the nitric oxide inhibitor NMMA could be used as an apoptotic inhibitor in the treatment of arthritis. Furthermore, it would have been reasonable to predict that NMMA would have successfully treated pathological calcification of cartilage given the teachings of Nurminskaya et al., Hashimoto et al. and Miyasaka et al. that inhibition of apoptosis is an appropriate therapeutic approach, and given the teachings of Miyasaka et al. that NMMA is such an apoptosis inhibitor. Thus, it would have been obvious to the person of ordinary skill to modify the teachings of Nurminskaya et al. by administering NMMA as taught by Hashimoto et al. and Miyasaka et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

It is reiterated that the instant claims only recite one active method step, i.e. administering NMMA. The remaining limitations recited by the dependent claims, i.e. wherein the inhibition of activation is accomplished by blocking production of a member selected from the group consisting of interleukins IL-1, IL-8, nitric oxide donor Noc-12, peroxynitrite generator Sin-1, tumor necrosis factor α (TNFα), and S100 family of proteins (recited by dependent claim 2), wherein the inhibition of activation is accomplished by blocking TNFα receptor-associated signaling factors (TRAFs), TRAF2 and TRAF6 (recited by dependent claim 3), and wherein the inhibitor is an inhibitor of IL- 1, Noc-12, Sin-1, tumor necrosis factor α (TNFα), and/or TNFα receptor-associated signaling factor (TRAFs), TRAF2 and TRAF6 (recited by dependent claim 6), are not active method steps. Rather, these are statements of phenomena that necessarily occur after the administration step. The combination of the prior art references above teach the active method steps recited by the claims; thus, claims 1-3, 5, 6 and 8-10 are rejected under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
23 February 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
February 26, 2009